II. REMARKS

Claims 1-37 are pending. Pursuant to a Restriction Requirement, claims 1-16, 18, and 24-37 have been canceled. Examined claims 17, 19 and 21-23 stand variously rejected under 35 U.S.C. § 112, first and second paragraphs and 35 U.S.C. § 102. Applicants note with appreciation that claim 20 is directed to allowable subject matter as it is free of the prior art and enabled by the specification as filed.

By amendment herein, claim 17 has been amended to indicate that the recombinant alphavirus particle contains one or more mutations (*e.g.*, substitutions, additions and/or deletions) in the E1 and/or E2 polypeptide. Support for this amendment can be found throughout the specification as filed, for example, on page 5, lines 4 to 9.

In view of the foregoing amendments and following remarks, Applicant respectfully requests reconsideration of the restriction requirement and of the application.

35 U.S.C. 112, Second Paragraph

Claim 17 stands rejected as allegedly vague in its recitation of "recombinant alphavirus particle." (Office Action, page 2). Although the Examiner acknowledges that most wild-type alphaviruses are not recognized to be able to infect human DC cells, it is maintained that "the metes and bounds of the recombinant alphavirus particles are not defined" because there are "so many alphaviruses in the art." (Office Action, page 2).

Because it is now plain, and would have been plain at the time of filing, that alphaviruses refer to any member of the *Alphavirus* genus, Applicants traverse this rejection. The standard is that the "definiteness of the language must be analyzed...in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore, supra.* A claim which is clear to one ordinarily skilled in the art when read in light of the specification, does not fail for indefiniteness. *Slimfold Mfg. Co. v. Kinkead Indus., Inc., supra.*

Nothing in the recitation of "a recombinant alphavirus particle" would be unclear to a skilled artisan in view of the specification as a whole. (see, *e.g.*, page 15, lines 17 to 28; page 21, lines 5 to 19). The specification clearly indicates that there are 26

known members of the Alphavirus (see, page 1, lines 16-23) and that these members are well characterized, readily available and very similar. (See, page 21, lines 5 to 19). Indeed, the specification notes that "Sindbis is the prototype member of the *Alphavirus* genus of the *Togaviridae* family. It's replication strategy is well characterized and serves as a model for other alphaviruses." (See, page 2, lines 8 to 10 of the specification). Numerous scientific publications by leading researchers in the field clearly establish that Sindbis is widely acknowledged to be the prototype member of the alphavirus genus. (See, for example, Smit et al., 2001, FEBS Lett 498(1):57-61 noting; Simpson et al., 1996, Virology, 222;464-469; Owen et al., 1996, J. Virol. 70:2757-2763; Carleton et al., 1997, J. Virol. 71:1558-1566; Lemm et al., 1994, EMBO J. 13:1925-1934 and Ryman et al., 2000, J Virol 74(7):3366-78)

Thus, in view of the teachings of the specification and teachings of the prior art, the recitation of "recombinant alphavirus particle" is clear to one skilled in the art and Applicants respectfully request withdrawal of this rejection.

35 U.S.C. § 112, First Paragraph, Enablement

Claims 17 and 21-23 stand rejected as allegedly not enabled by the specification as filed. In particular, it is alleged that the specification, while being enabling for recombinant Sindbis particles having a substitution at residue 160 of E2, does not reasonably enable any or all recombinant alphaviruses capable of infecting human dendritic cells (DCs). (Office Action, page 3).

Applicants traverse the rejection and supporting remarks.

The Breadth of the Claims

The Examiner maintains that it would require undue experimentation to practice the invention in any and all recombinant alphavirus vectors. (Office Action, page 3). In addition, it is asserted that Applicants should be limited to claims directed to the specific, exemplary embodiments described in the specification (*i.e.*, a recombinant Sindbis virus having Gly substituted for Glu at residue 160).

As a threshold matter, Applicants note that the pending claims do not encompass any and all recombinant alphaviruses, regardless of their ability to infect human dendritic cells. Rather, the claims at issue are directed to recombinant, modified alphavirus particles that have this ability. Further, it is specified that the alphaviruses contain a mutation in the E1/E2 glycoprotein region (as compared to wild-type). Disclosed in the specification are suitable recombinant alphaviruses (see, e.g., page 5, lines 4 to 12) and the fact that the ability to infect dendritic cells is imparted by mutations in the E1/E2 region. (See, page 5, lines 4-8). Also disclosed in the specification is the fact that all 26 known alphavirus types and subtypes include similar structures and polyproteins (including E2) and that Sindbis is the prototype alphavirus. (See, references and Background of the Invention). Thus, contrary to the Office's assertion, the claims are not unduly broad and, accordingly, limiting Applicants to claims directed solely toward their exemplified embodiments would be unduly restrictive.

Further, the law is settled that, for a claimed genus, representative examples together with a statement applicable to the genus as whole is sufficient to establish enablement if the skilled artisan would expect the claimed genus could be used in the manner set forth. *See, e.g.,* U.S. Patent and Trademark Office's Training Materials on Enablement, p. 29. In the pending case, the specification clearly contemplates and teaches that any alphavirus can be modified to infect human dendritic cells. See, *e.g.,* page 20, line 24 to page 21, line 19). Applicants' specification incorporates by reference (on page 12, lines 20-24) the teachings regarding the Alphaviruses in general and how it was known that these viruses are similar in phenotype and genotype. Indeed, Applicants exemplify aspects of their invention with Sindbis -- the prototype of an alphavirus. (See, *e.g.,* Example 1). The teachings of the specification (including Examples) readily enable one of skill in the art to select and identify mutations in the alphavirus genome (e.g., E2/E1 gene region) that confer human dendritic cell tropic phenotype and incorporate said mutations into recombinant alphavirus particles.

The question of enablement is what the specification teaches one of skill in the art. In this case, the specification teaches one of skill in the art how to make and use the precisely claimed invention. Simply put, one skilled in the art would have no trouble in

following Applicants' specification to make and test other embodiments falling within the scope of the claims. Applicants describe and demonstrate alphaviruses that infect human and murine cells, not only murine cells. The difference between such cells is repeatedly addressed by the art and the specification itself. Moreover, Applicants' methods for selection and testing suitable recombinant alphaviruses are set forth in the specification, for instance in the Examples. Because the specification provides ample guidance as to identification and selection of alphaviruses that can be modified to infect human DCs as claimed, undue experimentation would not be required to practice the invention throughout its scope. Accordingly, withdrawal of the rejection is in order.

The Prior Art Does not Establish Unpredictability

Applicants also disagree with the assertion that various references disclose a number of caveats that make it difficult for the skilled artisan to predict "whether any or all recombinant alphaviruses can infect human DCs." (Office Action, page 3).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). Applicants are under no legal obligation to make a "prediction" concerning any and all alphaviruses that are useful in the claimed methods. Further, no such prediction is necessary -- one of ordinary skill in the art, following the teachings of the present specification, could select, construct and/or test candidate recombinant alphaviruses for their ability to infect human dendritic cells as described in the specification. As noted above, techniques for modifying and/or identifying recombinant alphavirus particles that infect human DC are fully described and exemplified in the specification (see, *e.g.*, Example 1). Following these teachings would not require extensive or undue experimentation and, indeed, such techniques are well within the ability of one having ordinary skill in the art in view of the specification's teachings.

Furthermore, the art cited by the Examiner does not establish that it would require undue experimentation for a skilled artisan to make and use the claimed invention. Neither Tucker nor MacDonald in any way address infection of human

dendritic cells with alphaviruses - a major problem solved by Applicants. With regard to Gardner et al. (2000), Applicants note the Examiner has improperly taken a single statement out of context. Indeed, any discussion in Gardner relating to toxicity is irrelevant to examined claims 17 and 19-23 (directed to recombinant alphaviruses that can infect human dendritic cells). Gardner refers to an experiment attempting to determine whether cell surface heparin sulfate binding is impacted by the E2 amino acid substitution in a Sindbis particle. In these experiments, enzymatic treatment of the DCs prior to infection with alphavirus particles was found to be toxic. Thus, any discussion relating to toxicity in this reference is irrelevant to the claims at issue. Further, Gardner et al. state that "these data illustrate the tremendous potential of using a directed approach in generating alphavirus vaccine vectors that target and activate antigen-presenting cells, resulting in robust antigen-specific immune responses." (See, last sentence of the Abstract). Thus, the art cited by the Office in no way establishes unpredictability of the subject matter of claims 17 and 19-23.

In view of the foregoing, the rejections under section 112, first paragraph are improper and Applicants respectfully request these rejections be withdrawn.

35 U.S.C. § 102

Claims 17, 19 and 21-23 stand rejected under 35 U.S.C. 102(b) as allegedly anticipated by WO 97/24447 (hereinafter "Song"). These claims are also rejected under 35 U.S.C. 102(a) as allegedly anticipated by Bungener. Song is cited for teaching a recombinant alphavirus vector that can target human dendritic cells. (Office Action, page 5). Bungener is cited for teaching the use of a Semliki Forest virus to infect human and murine dendritic cells. (Office Action, page 5).

Applicants traverse the rejections and supporting remarks.

It is axiomatic that an anticipatory reference must disclose each and every element of the claims. *Hybritech v. Monoclonal Antibodies,* 231 USPQ 81 (Fed. Cir. 1986). Moreover, the single source cited by the Office must also disclose all of the claimed elements arranged as in the claims. *See, e.g., Richardson v. Suzuki Motor Co.,* 9 USPQ2d 1913 (Fed. Cir. 1989). It is also well-settled that in order to constitute an

anticipatory reference, the cited document must contain an enabling disclosure. *Chester v. Miller*, 15 USPQ2d 1333, 1336 n.2 (Fed. Cir. 1990); see also, *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1011 (Fed. Cir. 1991). In other words, the reference must teach one of skill in the art how to practice the claimed invention, without undue experimentation.

Song does not describe or demonstrate each and every element of the claims 17, 19 and 21-23. The claims are directed to recombinant alphavirus vectors that infect human dendritic cells. The alphaviruses themselves are modified (*e.g,* structurally so as to change amino acid sequence in E1 or E2) in order to be infectious for human DCs. Song cannot anticipate these because it is does not disclose alphaviruses that, on their own, infect human DC. Rather, Song requires that an additional "targeting element" be used. (See, page 22, lines 1 to 12). These targeting elements are separate from the alphavirus particle. As is readily apparent upon reading Song, modification of the alphavirus itself was not contemplated. Thus, Song cannot anticipate the pending claims.

For its part, Bungener cannot anticipate pending claims 17, 19 and 21-23 because it does not disclose SFV particles that infect human dendritic cells. First and foremost, Applicants note that Bungener reports transfection efficiency of 0.25%. This extremely low level of "positive" DC, referred to as transfection efficiency, would not be considered by a skilled artisan to be above background levels. (See, *e.g.,* references including transfection studies of DC using non-alphavirus vectors attached as Exhibit A, specifically Figure 1B of Trevor et al. (2001) *Cancer Immunol Immunother* 50:397-407; Figure 3B of Strobel et al. (2000) *Human Gene Therapy* 11:2207-2218; Figure 3B of Rea et al. (2001) *J. Immunol.* 166:5236-5244; and Table 5 of Movassah et al. (1999) *Human Gene Therapy* 10:175-187). Indeed, Bungener et al. conclude from their own studies that dendritic cells are resistant to transfection with SFV. (See, last sentence of Abstract).

Moreover, background levels of "positive" DC cannot create an assumption that the particles are actually infectious for DCs as claimed by Applicants. At the time the application was filed, it was known by persons of ordinary skill in the field of viral biology that many virions bind non-specifically to the surface of a host cell and are internalized. Indeed, as summarized in "Fundamental Virology", eds. Fields and Knipe

(1990), attached hereto as Exhibit B, non-specific binding is a well-known occurrence to those working in this area:

> "The first event in viral infection of the host cell is binding of the virus to the cell surface. The cell-surface molecule with which the virus first interacts or binds is called the *cell receptor*. It has been difficult to define the physiological receptor for viruses for several reasons: (a) a virus may bind specifically or non-specifically to a number of surface molecules; (b) a virus is a large ligand that can interact with a large surface area on the cell, thereby giving numerous cellular molecules that may cofractionate with a virus-receptor complex; or (c) a virus may have alternate receptors on individual or different cells. ... Thus, as their receptors, viruses can utilize cell-surface molecules that normally serve the host cells as receptors for other molecules." (Fundamental Virology, pages 269-270, emphasis added).

It was (and is) well known that dendritic cells, in particular, take up foreign particulates into the cell through a variety of non-specific processes, for example, phagocytosis. Thus, it is plain that background level of transfection of a DC cannot establish that the particles are infectious. In fact, the authors of the Bungener abstract themselves use the term "infection"in reference to previous studies, while choosing primarily to characterize their own work as "transfection" studies. (See, Title and last sentence). In sum, Bungener's study showing background levels of transfection into human DC cannot properly be used to reject claims directed to human DC-infectious alphavirus particles.

Simply put, neither Song nor Bungener teach or suggest alphavirus particles that infect human DC. Therefore, these references do not anticipate the pending claims and withdrawal of these rejections is in order.

III. CONCLUSION

For the reasons state above, Applicant respectfully submits that the pending claims define an invention which is novel and fully enabled by the specification.

Accordingly, Applicant requests that the rejection of the claims be withdrawn, and that the application proceed to allowance.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648.

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Version Showing Changes Made to Claims

17. (Amended) A recombinant alphavirus particle which infects human dendritic cells, said recombinant alphavirus particle comprising one or more amino acid mutations in the E1 or E2 polypeptide as compared to wild-type, with the proviso that said recombinant alphavirus particle is not derived from ATCC # VR-2526.

Currently Pending Claims

1 to 16. Withdrawn

17. (Amended) A recombinant alphavirus particle which infects human dendritic cells, said recombinant alphavirus particle comprising one or more amino acid mutations in the E1 or E2 polypeptide as compared to wild-type, with the proviso that said recombinant alphavirus particle is not derived from ATCC # VR-2526.

18. Withdrawn.

19. The recombinant alphavirus particle of claim 17 or 18 wherein said alphavirus is a Sindbis virus.

20. The recombinant alphavirus particle according to claim 19 wherein said alphavirus has an amino acid substitution at E2 residue 160, as compared to wild-type Sindbis virus.

21. The recombinant alphavirus particle according to claim 17 or 18 wherein said alphavirus is Semliki Forest virus.

22. The recombinant alphavirus particle according to claim 17 or 18 wherein said alphavirus is Ross River virus.

23. The recombinant alphavirus particle according to claim 17 or 18 wherein said alphavirus is Venezuelan equine encephalitis virus.

24 to 37. Withdrawn.